AADA 64-150

Eon Labs Manufacturing Inc.
Attention: Yau-Kit Lam
227-15 North Conduit Avenue
Laurelton, NY 11413

JUL 16 1996

Dear Mr. Lam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Rifampin Capsules, 300 mg. This correspondence which supersedes our previous correspondence dated June 26, 1996, modifies the dissolution specification as provided in USP 23, supplement 3; page 2976.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be incorporated into your manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of 0.1N HCl at 37°C using USP 23 apparatus 1 (basket) at 100 rpm. The test drug product should meet the following specifications:
>
> > Not less tha(b)4f the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

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Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OCT 1 2 1995

Rifampin 300 mg Capsules
300 mg Capsules
ANDA # 64-150
Reviewer: Sikta Pradhan, Ph.D.
WP #64150SD.495

Eon Labs Manufacturing, Inc.
Laurelton, NY
Submission Date:
April 12, 1995

REVIEW OF A BIOEQUIVALENCE STUDY

Introduction

Rifampin is a semisynthetic derivative of rifamycin B, an antibiotic produced by certain strains of Streptomyces mediterranei. Rifampin is used in the treatment of both tuberculosis and the meningococcal carrier state. It inhibits DNA-dependent RNA polymerase activity in susceptible cells. It interacts with bacterial RNA polymerase but does not inhibit the mammalian enzyme.

Rifampin is readily absorbed from the gastrointestinal tract. The peak plasma drug concentration occurs within 2 to 4 hours after oral administration. The plasma half-life of rifampin following a 600 mg oral dose in healthy adult subject is about 3 hours. More than 80% of the drug is bound to plasma proteins. Rifampin is widely distributed into most body tissues and fluids. Absorption of rifampin is delayed and reduced when it is given with food. The drug is rapidly eliminated in the bile and undergoes progressive enterohepatic circulation and deacetylation to the primary metabolite, 25-desacetyl-rifampin. This metabolite is microbiologically active. About 30% or less of the dose is excreted as rifampin or metabolites.

The drug is currently available as Rifadin^{R}, 150 mg and 300 mg capsules manufactured by Marion Merrell Dow. The usual daily dosage of rifampin is 600 mg to 1200 mg depending on the indication.

Objective:

The objective of the study is to compare the relative bioavailability of Rifampin 300 mg capsules, manufactured by Eon Labs., Inc. with that of Rifadin^{R} 300 mg capsules, manufactured by Marion Merrell Dow, in healthy, male volunteers dosed under fasting condition.

In-Vivo Study

The study was conducted under the direction of (b)4 - Confidential Business

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Manager, [redacted].

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Study Dates:

Date of Samples Collection: November 26, 1994 (Period I)
December 03, 1994 (Period II)

Study Design

A randomized 2-way crossover, single dose bioequivalence study on the test product, Rifampin, 300 mg capsule (Eon Labs) and reference product, Rifadin^{R} 300 mg capsule (Marion Merrell Dow) was conducted in healthy adult male volunteers according to the protocol #930852.

Subject: Thirty-six (36) volunteers and two (2) alternates between 20-45 years of age and within ± 15% of their ideal body weight according to Metropolitan life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Test (hematology, blood chemistry, urinalysis, etc.) The subjects were restricted from all medications for one week prior to the first drug administration until after the study was completed. The volunteers were not allowed to consume alcohol- or xanthine-containing beverages and food for 24 hours prior to the initiation of the study until after the completion of the study. The subjects were randomly divided into two dosing groups of equal numbers.

Treatments:

A. 300 mg x 2 Rifampin capsules (Eon Labs.), Lot #941101, Potency 100.1%, Lot size: Not reported.

B. 300 mg x 2 Rifadin^{R} capsules (Marion Merrell Dow), Lot #3405CM, Potency 98.5%, Exp. Date: 4/95.

Dose Administration:

A single dose of 600 mg (test or reference) was administered with 240 mL of water. A mouth check was performed to assure ingestion.

Drug Washout Period: 7 days

Meal and Food Restrictions:

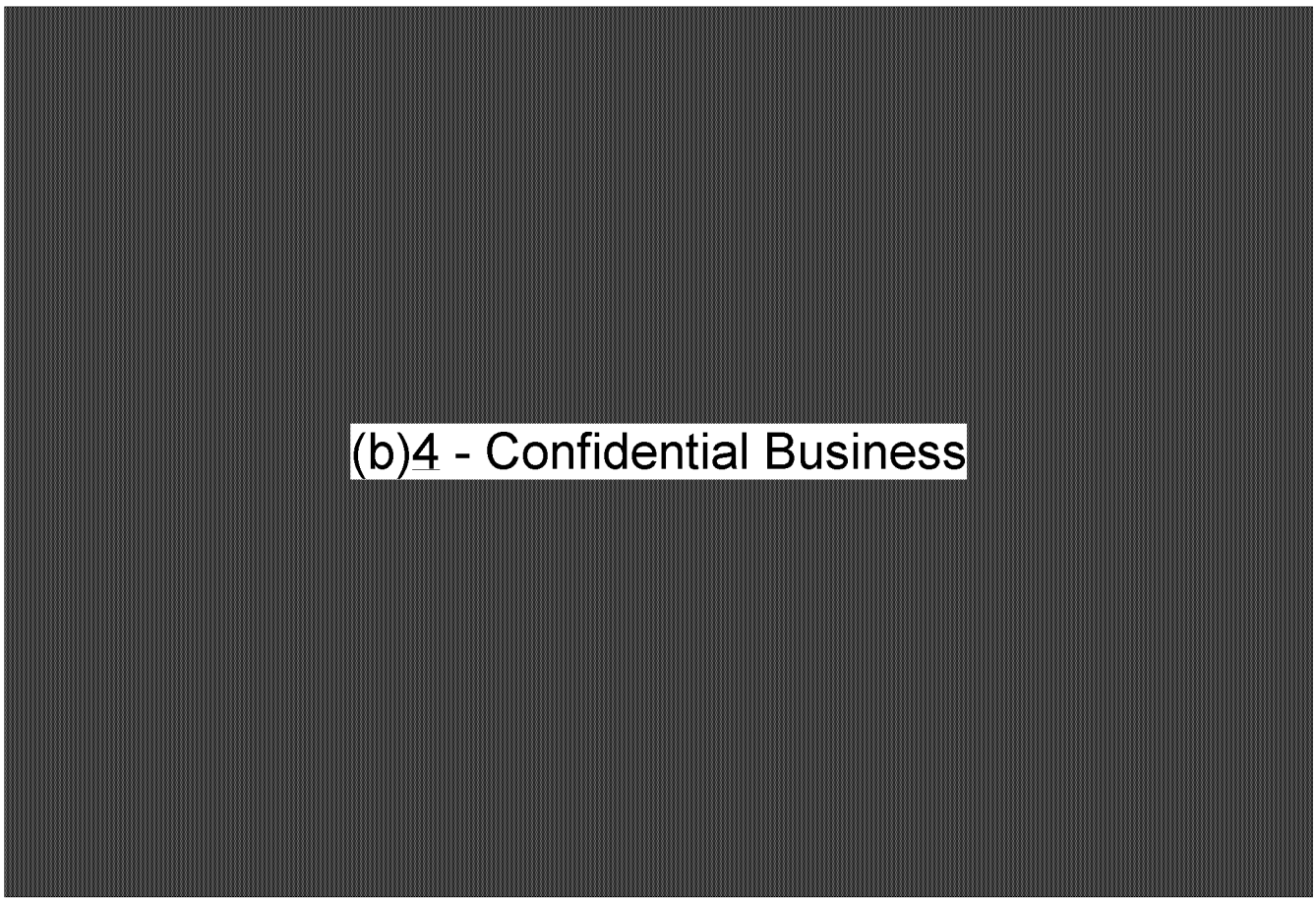
All volunteers fasted for 10 hours prior to and 4 hours after drug administration. No fluids were allowed from 2 hour before dosing

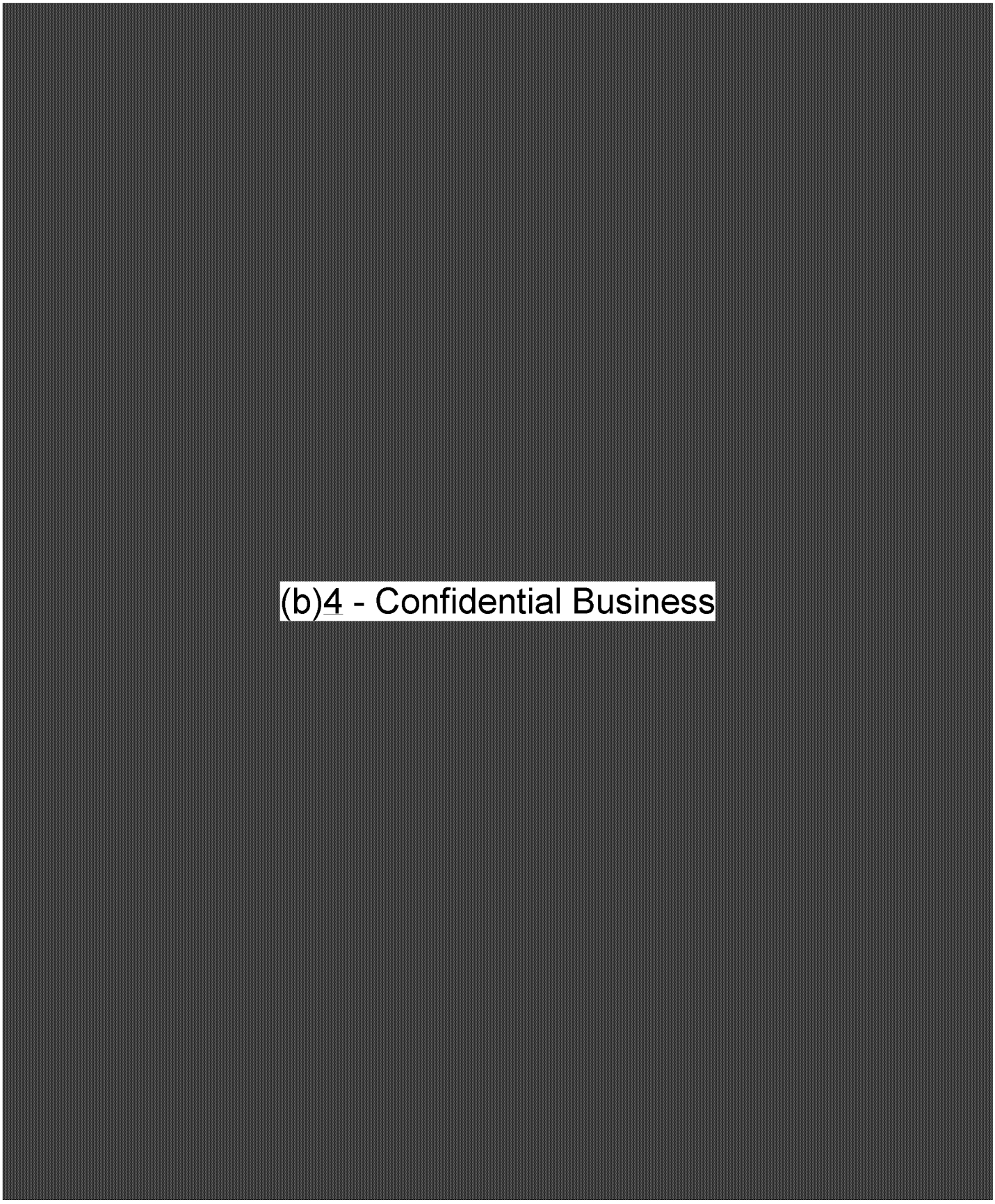
until 4 hours after each dose. Water was given ad lib after 4 hours of dosing. Standard meal was served after 4 hours of dosing. No caffeine-containing food or beverages were served during the first 24 hours. All subjects were confined from 10 hours pre-dose to 24 hours post-dose.

Blood Samples Collection

Ten (5x2) mL blood samples were collected in vacutainers containing EDTA at 0 (pre-dose), and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16 and 24 hours post-dose. Due to the sensitivity of rifampin to ultraviolet (UV) light, blood samples were collected and processed under UV filtered light bulbs to minimize their UV exposure. The collected blood samples were cooled in an ice bath and centrifuged under refrigeration as soon as possible. For pre-dose samples, 2 mL of plasma was transferred to tubes containing 20 µL of L-ascorbic acid (50 mg/mL), and for all post-dose samples, 1 mL of plasma was transferred to tubes containing 10 µL L-ascorbic acid (50 mg/mL), and were mixed thoroughly by vortexing. All plasma samples were stored at -80^0 C until analyzed.

Assay Methodology

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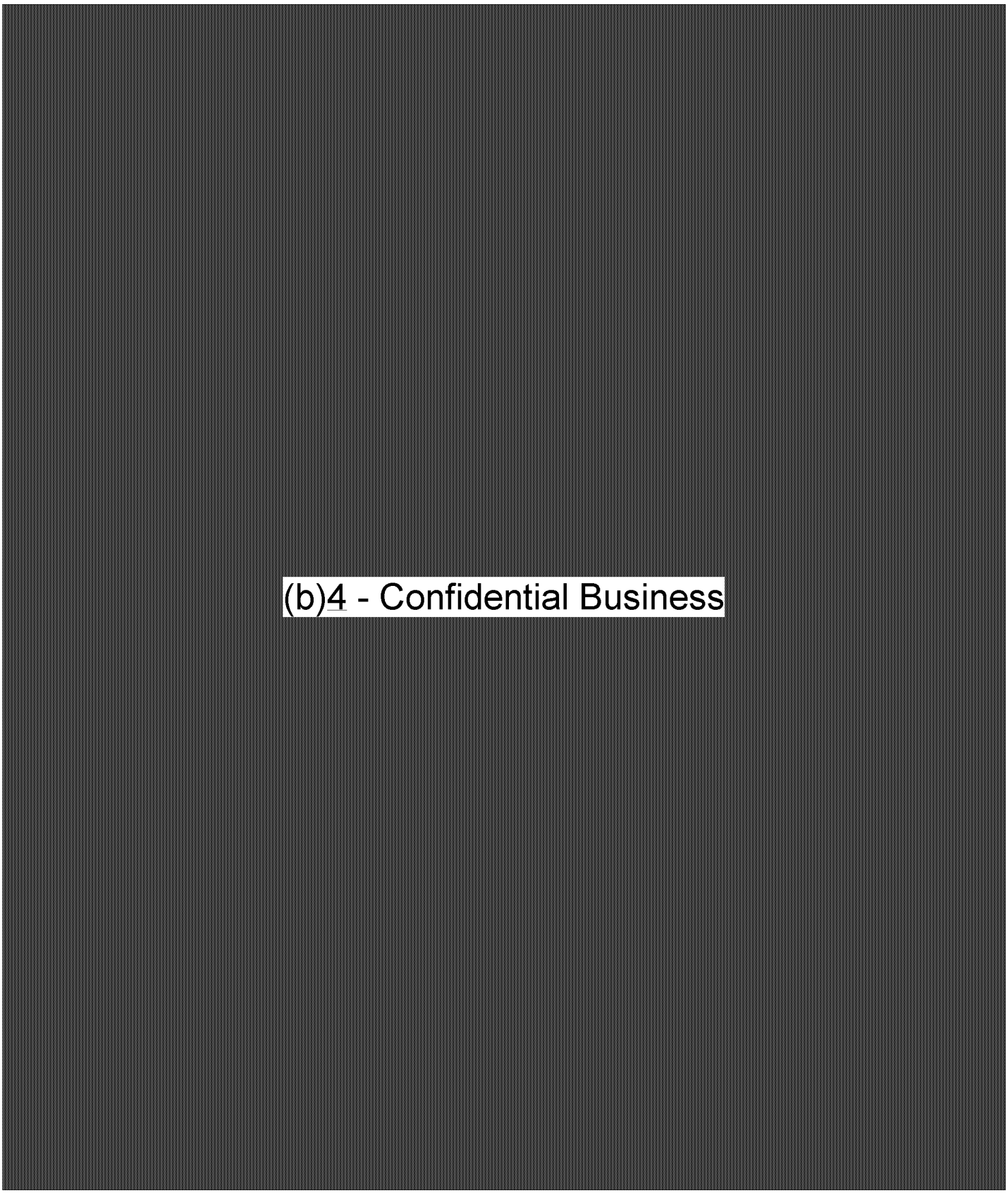
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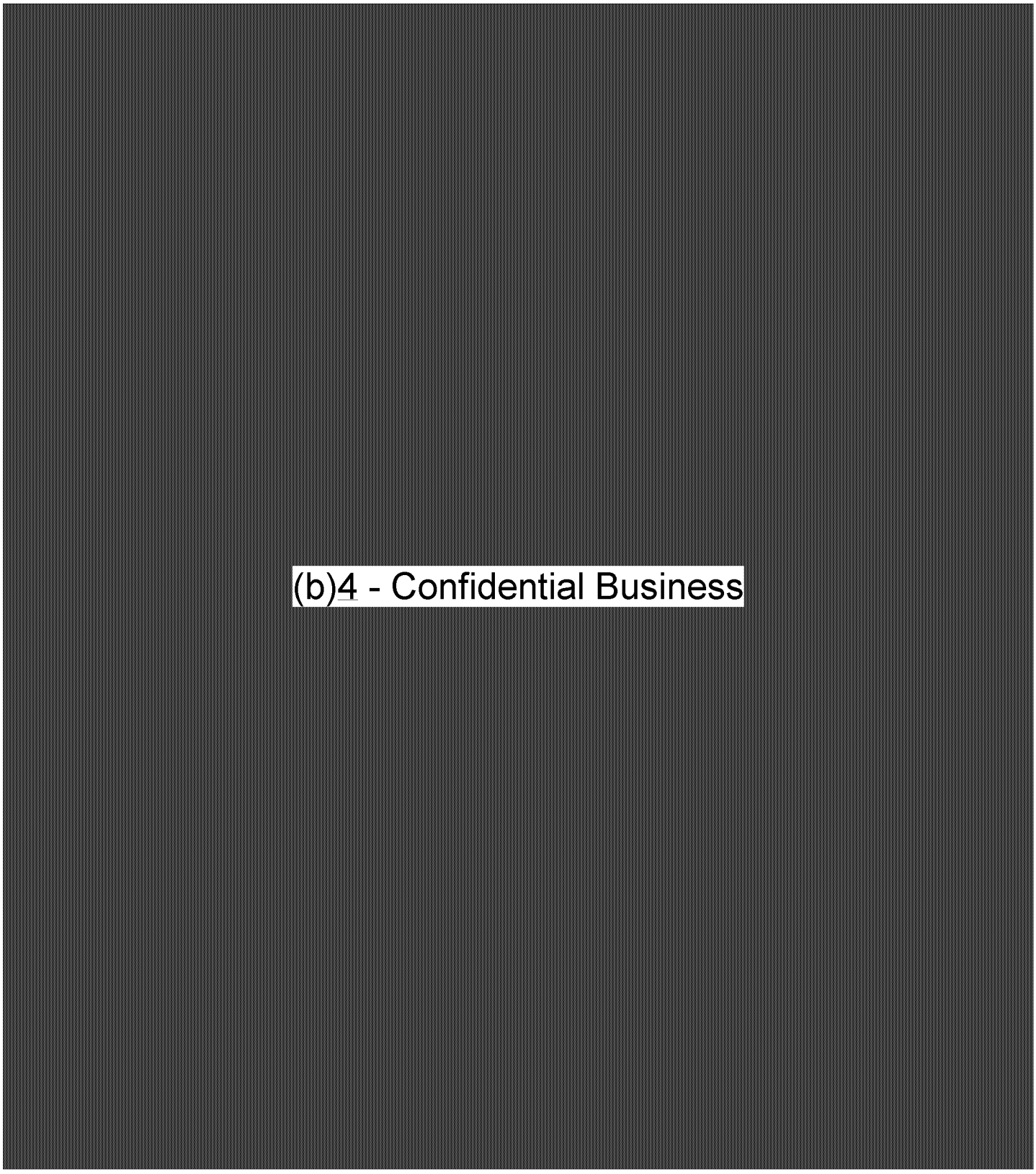
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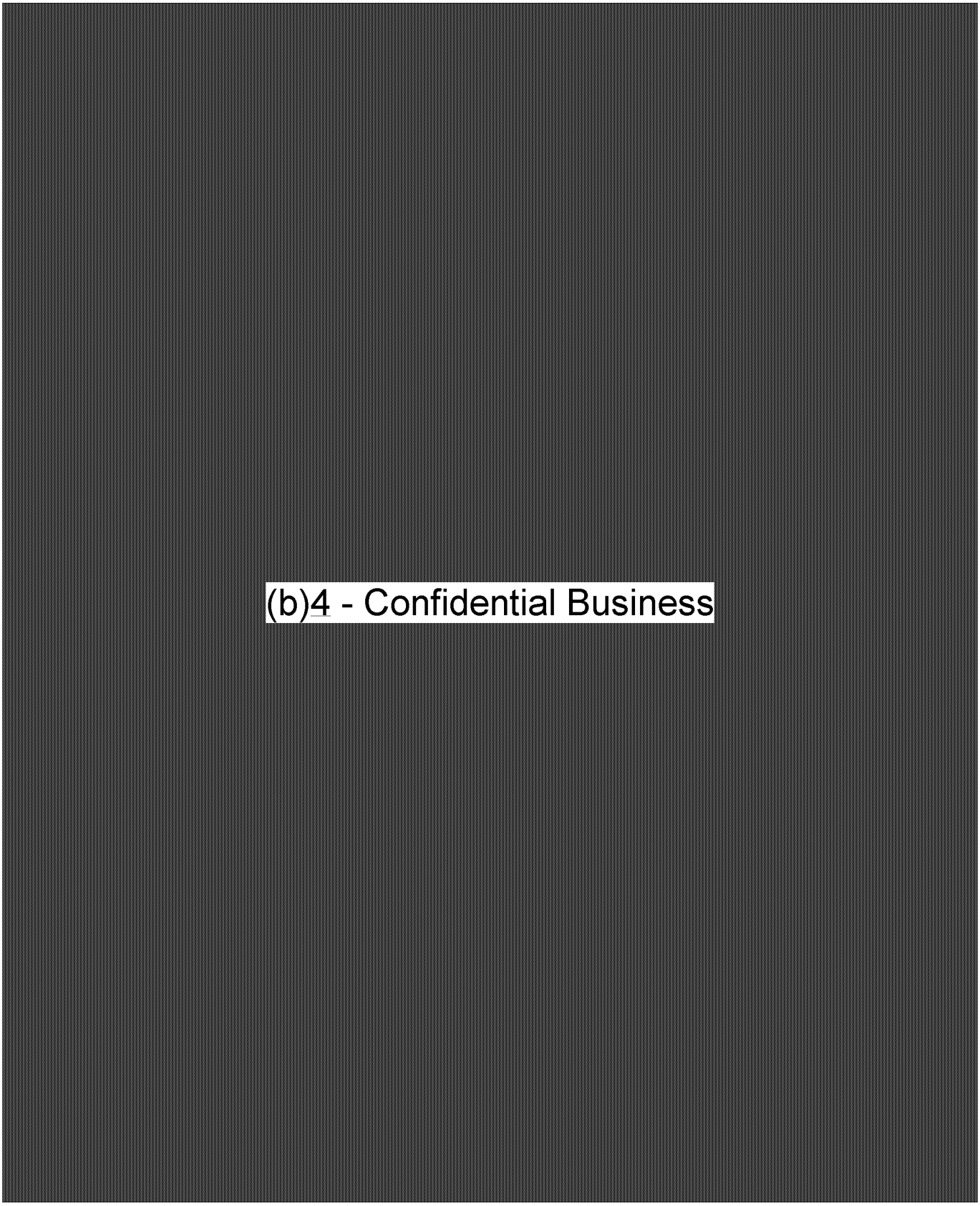
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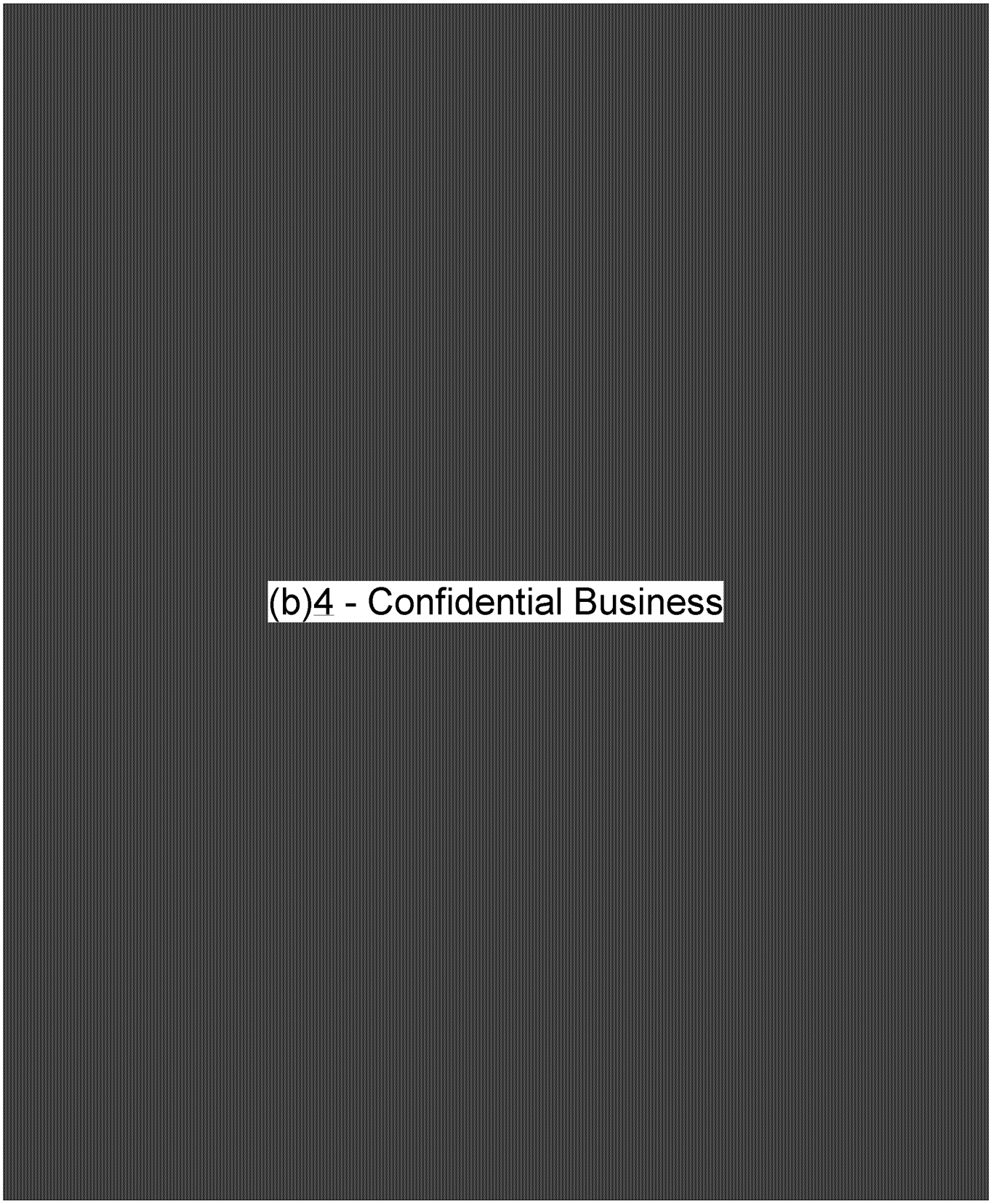
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Pharmacokinetic Methodology

Area under the curve(0-t) and AUC(0-inf) were calculated from plasma data of 36 subjects by the linear trapezoidal method. The elimination parameters for each subject in each dosing group were derived. Tmax, the time of the maximum measured plasma concentration and Cmax, the maximum measured plasma concentration were also reported. The mean pharmacokinetic parameters are presented in Table 3 and Table 4, respectively.

Statistical Analyses

Analysis of variance (ANOVA) was performed at an alpha=0.05 using the GLM procedure of SAS on the untransformed and log-transformed (only for AUC0-t, AUCinf and Cmax) pharmacokinetic data. The ANOVA model included sequence, subjects nested within sequence, period and drug formulation as factors. The significance of the sequence effect was tested using the subjects nested within sequence as the error term. The 90% confidence intervals for the differences between formulations were calculated for AUC0-t, AUC0-inf and Cmax by using two one-sided t-test.

Results:

Mean plasma rifampin and 25-desacetyl rifampin levels of 36 subjects are presented in Table 1 and Table 2, respectively.

Table 1
Mean Plasma Rifampin Levels (µg/mL)

Time (hour)	Test (A) 2X300mg Tab (Eon) Lot # 941101(Subj=36)	Reference (B) 2X300mg Rifadine^{R} Tab (M.M.Dow) Lot # 3405CM (Subj=36)	A v s B Diff **Signf.
0	0	0	
0.50	2.49 (117*)	1.31 (148)	
1.0	8.77 (49)	8.70 (37)	
1.5	9.32 (36)	9.80 (31)	
2.0	8.95 (32)	9.15 (25)	
2.5	8.51 (24)	8.66 (23)	
3.0	7.90 (23)	7.92 (25)	
4.0	6.76 (22)	6.71 (24)	
6.0	4.29 (25)	4.19 (24)	
8.0	3.08 (35)	2.97 (31)	
10.0	1.89 (44)	1.80 (40)	
12.0	1.16 (59)	1.09 (52)	
16.0	0.35 (114)	0.30 (108)	
24.0	0.01 (600)	0.02 (353)	

* Coefficient of Variation
** Statistical Data Not Provided

Table 2
Mean Plasma 25-Desacetyl Rifampin Levels (μg/mL)

Time (hour)	Test (A) 2X300mg Tab (Eon) Lot # 941101(Subj=36)	Reference (B) 2X300mg Rifadine^{R} Tab (M.M.Dow) Lot # 3405CM (Subj=36)	A v s B Diff **Signf.
0	0	0	
0.50	0.04 (204*)	0.01 (359)	
1.0	0.44 (60)	0.41 (58)	
1.5	0.74 (47)	0.77 (47)	
2.0	0.90 (41)	0.93 (39)	
2.5	0.98 (34)	1.02 (36)	
3.0	1.04 (31)	1.08 (38)	
4.0	1.12 (28)	1.15 (36)	
6.0	0.91 (30)	0.91 (37)	
8.0	0.74 (36)	0.74 (46)	
10.0	0.43 (44)	0.42 (56)	
12.0	0.26 (56)	0.25 (70)	
16.0	0.08 (116)	0.07 (140)	
24.0	0.00 (00)	0.004(600)	

* Coefficient of Variation
** Statistical Data Not Provided

Table 3
Mean Pharmacokinetic Parameters for Rifampin in Plasma

Parameters (*Arithmetic Means)	Test(A) (Subj=36)	Ref.(B) (Subj=36)	A/B (%)	Intrasubject variability (%)
AUC_{0-T} (μg.hr/mL)	57.63 (30**)	56.65 (27)	103	10.8
AUC_{0-inf} (μg.hr/mL)	59.91 (30)	58.52 (27)	104	9.8
C_{MAX} (μg/mL)	10.78 (24)	10.72 (23)	102	13.6
T_{max} (hour)	1.557(46)	1.486(32)		
t1/2 (hour)	2.91 (19)	2.84 (18)		
KE (1/hour)	0.2458 (17)	0.2513 (16)		

Parameters (Using LSM)	Test(A)	Ref.(B)	A/B (%)	90% C.I.
$LnAUC_{0-T}$ (μg.hr/mL)	4.011980	4.003321	101	**97; 105**
Geometric mean	55.26	54.78		
$LnAUC_{0-inf}$ (μg.hr/mL)	4.052288	4.037062	101	**98; 105**
Geometric mean	57.53	56.66		
LnC_{MAX} (μg/mL)	2.346180	2.348892	100	**94; 105**
Geometric mean	10.45	10.4		

* In this case, arithmetic means and least squares means are same.
** Coefficient of Variation

Table 4
Mean Pharmacokinetic Parameters for 25-Desacetyl Rifampin in Plasma

Parameters (Using Arithmetic Means)	Test(A) (Subj=36)	Ref.(B) (Subj=36)	A/B (%)	Intrasubject Variability (%)
AUC_{0-T} (μg.hr/mL)	8.93 (33**)	9.10 (45)	98	14.3
AUC_{0-inf} (μg.hr/mL)	9.61 (32)	9.73 (42)	99	13.1
C_{MAX} (μg/mL)	1.15 (28)	1.17 (36)	98	11.5
T_{max} (hour)	3.58 (23)	3.69 (20)		
t1/2 (hour)	2.92 (17)	2.86 (25)		
KE (1/hour)	0.2438 (17)	0.2558 (22)		

Parameters (Using LS Means)	Test(A)	Ref.(B)	A/B (%)	90% C.I.
$LnAUC_{0-T}$ (μg.hr/mL)	2.129931	2.112140	101	**97; 105**
Geometric mean	8.41	8.27		
$LnAUC_{0-inf}$ (μg.hr/mL)	2.209838	2.189779	101	**98; 105**
Geometric mean	9.11	8.93		
LnC_{MAX} (μg/mL)	0.091861	0.089399	100	**94; 105**
Geometric mean	1.10	1.10		

* Coefficient of Variation

For Parent Product

Both test and reference drugs produced peak concentration of rifampin between 1 to 2 hours after their administration. There were 2-4% differences between the test and reference products in AUC_{0-T}, AUC_{0-inf} and C_{MAX} values. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

For Metabolite

Both test and reference drugs produced peak concentration of 25-desacetyl rifampin at about 4 hours after their administration. There was only 1% difference between the test and reference products in AUC_{0-T}, AUC_{0-inf} values. There was no difference in C_{MAX}. The 90% confidence intervals for $LnAUC_{0-T}$, $LnAUC_{0-inf}$ and LnC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

In-Vitro Dissolution:

The firm has conducted an acceptable dissolution testing on Rifampin Capsules. The dissolution testing data are presented in Table 5 below:

Drug (Generic Name): Rifampin Capsules Firm: Eon Manufacture Lab.
Dose Strength: 300 mg
ANDA # 64-150 Submission Date: April 12, 1995

Table -5 In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket X Paddle __ RPM 50 No. Units Tested: 12

Medium: 0.1N HCl Volume: 900 ml

Reference Drug: Rifadin[R] (Marion Merrell Dow)

Assay Methodology: (b)4 -

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 941101 Strength (mg) 300 Mean % Dissolved	Range	(CV)	Reference Product Lot # 3405CM Strength (mg) 300 Mean % Dissolved	Range	(CV)
15	48.4	(b)4 -	(10.7)	19.2	(b)4 -	(41.2)
30	100.6	Confidentia	(4.4)	80.5	Confidentia	(8.0)
45	101.9	Business	(2.7)	99.0	Business	(4.3)
60	102.4		(2.6)	99.8		(4.0)

Formulations:

The composition of Rifampin Capsules, 300 mg (lot #941101) is presented below:

Ingredients	**Strengths (mg/ capsule)**
Rifampin, USP	300.0
Microcrystalline Cellulose, NF	[redacted]
Corn Starch, NF	
Colloidal Silicon Dioxide, NF	
Docusate Sodium [redacted] / Sodium Benzoate [redacted]	(b)4 -
Talc, USP	onfident
Magnesium Stearate,NF	Busines
(net Capsule Fill Weight)	
#1 Gelatin Capsule, [redacted] orange opaque cap & body, imprinted "E 799" in black ink	[redacted]
Total Capsule Weight	**437.0**

[redacted]

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Comments:

1. The comparative in vitro dissolution testing conducted on the test and reference products is acceptable. However, the in vivo bioequivalence study conducted on the test and the reference products has been found to be incomplete.

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5.

6. [redacted] (b)4 - Confidential Business [redacted] to be

7. The firm should inform the Agency the Lot size of the test product used in the in vitro dissolution testing and in vivo bioequivalence study.

8. There were a number of blood collections that deviated from the target times due to late arrival of some subjects. The firm should be requested to provide the reason for late arrival of each subject.

9. The firm should be requested to submit all statistical analyses conducted on the test and reference samples collected at each sampling time.

Recommendation:

The in vivo bioequivalence study conducted by Eon Labs Manufacturing Inc. on its 300 mg Rifampin Capsules of Lot #941101, versus the reference product, Rifadin^{R} 300 mg Capsules manufactured by Marion Merrell Dow Inc. has been found to be incomplete by the Division of Bioequivalence for the reasons stated in Comments #1 - 9 above.

[redacted] /S/

Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

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Concu[redacted] Date:----------

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 64-150 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Pradhan), Drug File, Division File.

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